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Comments on Proposed Fish Two-Generation Toxicity Test

Endocrine Disruptor Methods Validation Subcommittee
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Should prevalidation evaluate the increased sensitivity of a two-generation design over the existing fish full life-cycle standard practice?

- In principle, yes. EPA must be able to demonstrate a significant need as well as "value added" before a new test and/or endpoint is considered as a regulatory requirement.
- That being said, EPA's current requirement for a multiplicity of animal tests for the same or similar endpoint(s) is redundant and unacceptable
  - e.g., pesticide AI's that have already undergone fish full life-cycle, mammalian 2-gen. studies, etc., and HPV chemicals that are currently undergoing 1-gen. repro/developmental studies, potentially being required to undergo very similar studies under the EDSP.
- Therefore, as a matter of policy, EPA program offices must better coordinate their chemical assessment efforts in order to prevent such obvious duplication.

Should prevalidation demonstrate the sensitivity and reproducibility for each species in the recommended protocol?

- From a strictly scientific perspective, yes, because it would be unwise to simply assume that data from one species are generalizable to another.
- On a policy level, however, it would be inappropriate for EPA to proceed into prevalidation of a test of this magnitude with four species. A single species is more than enough. As the DRP suggests, “pre-selection of one of the four species…would limit the number of demonstration trials for full optimization…” (p. 2)

Issues of concern regarding the DRP

- Methodological limitations
  - "full life-cycle exposures…can result in unexpected interruptions in exposure as a result of test substance behavior in water or equipment malfunction" (p. 25)
  - "continuous exposure of P, F1 and juvenile F2 generations has not been reported" (p. 27; also pp. 28-31)
  - "methods of sexual differentiation are established for zebrafish and medaka, but are not published for fathead minnow and sheepshead minnow" (p. 101)
- Route of exposure
  - Testing of poorly soluble compounds in aquatic systems is highly questionable. EPA itself has recommended against testing of substances with a log $K_{OW} \geq 4.2$ in fish because conditions of such studies are both biologically and toxicologically irrelevant (HPV Test Rule, 2000, *65 Fed Reg*, 81658-81685)
  - Use of solvents to enhance exposure to hydrophobic compounds is questionable.
  - Major identified confounds associated with oral exposure route.

Issues of concern regarding the DRP

- Dose selection and sample size
  - The DRP's proposed use of "at least five treatment levels" (p. 30) is excessive and should be reduced.
  - The number of replicates and control groups (e.g., solvent, dilution water, etc.) should be minimized.
  - The recommended "100 embryos per replicate" is unacceptably high and, as the DRP acknowledges, "twice the number previously recommended by regulatory agencies" (p. 34).

Concluding thoughts

- EPA's development of two-generation / life-cycle toxicity studies in five separate taxonomic groups is redundant and unnecessary.
- Immediate consideration should be given to reducing the scope of Tier 2 to the single most sensitive species, and discontinuing efforts to develop and validate multigenerational studies in others.